

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁶ : A61K 9/20, 9/48, 9/50	A1	(11) International Publication Number: WO 96/41617 (43) International Publication Date: 27 December 1996 (27.12.96)
(21) International Application Number: PCT/EP96/02495 (22) International Filing Date: 5 June 1996 (05.06.96) (30) Priority Data: MI95A001223 9 June 1995 (09.06.95) IT (71) Applicant (for all designated States except US): APR APPLIED PHARMA RESEARCH S.A. [CH/CH]; Via Giulia, 43, CH-6855 Stabio (CH). (72) Inventors; and (75) Inventors/Applicants (for US only): CONTE, Ubaldo [IT/IT]; Viale Taramelli, 12, I-27100 Pavia (IT). MAGGI, Lauretta [IT/IT]; Via Folperti, 3, I-27100 Pavia (IT). REINER, Alberto [IT/IT]; Via Mentana, 23/B, I-22100 Como (IT). (74) Agents: DRAGOTTI, Gianfranco; Saic Brevetti s.r.l., Galleria San Babila, 4/D, I-20122 Milano (IT) et al.		(81) Designated States: CA, KR, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: SOLID PHARMACEUTICAL FORM FOR ORAL USE (57) Abstract By combining the same active ingredient in a form which is readily soluble in water or aqueous liquids and in a delayed and programmable release form in the same solid pharmaceutical form for oral administration, preferably in the form of a double-layered tablet, high plasma levels are obtained immediately after administration which lead to a consequently rapid therapeutic effect and the maintenance of high plasma levels over a prolonged period after administration. The two forms of active ingredient are accompanied by suitable adjuvants and excipients which are capable of causing the rapid disintegration of the layer containing the active ingredient in a readily soluble form and the delayed release of the active ingredient in the delayed release form.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Larvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

SOLID PHARMACEUTICAL FORM FOR ORAL USE

The present invention relates to solid pharmaceutical forms which can be used principally orally and which are capable of releasing the active substance(s) contained therein in accordance with release kinetics which may advantageously be
5 predetermined by means of suitable in vitro experiments.

More specifically, the invention relates to solid pharmaceutical forms, especially tablets, which are intended principally for the oral administration of active ingredients that are poorly soluble in water or in an acid medium and that are normally characterised by an erratic therapeutic effect because absorption is greatly limited by
10 the solubility of the active substance.

The aim of the present invention is preferably to introduce into a carrier active ingredients, such as pain-killing, anti-inflammatory and anti-angina drugs, and, in general, other active ingredients which are required to exhibit not only an immediate therapeutic effect but also the maintenance of activity over a more prolonged period.

15 There is a great multiplicity of pharmaceutical forms permitting the administration of drugs which are to remedy acute clinical pictures, such as those marked by painful symptoms. A typical example is thus that of drugs having a pain-killing and/or anti-inflammatory activity, which will be the example principally referred to hereinafter, but it should be understood that this is in no way to be regarded as limiting.

20 One of the main requirements which must be met by a pharmaceutical form which contains an active ingredient having a pain-killing, anti-angina and analgesic activity in general is that it must bring about efficient levels of plasma rapidly and thus likewise the rapid onset of the desired therapeutic effect.

In most cases, oral administration involves a substantial delay in the onset of the
25 therapeutic effect compared, for example, with parenteral administration, because the solid pharmaceutical form (capsule or tablet) has to undergo processes of disintegration and then dissolution of the active ingredient contained therein. In fact, only the dissolved or solubilised active substance may be absorbed because, by the absorption, levels of plasma result which, from a certain plasma concentration, can
30 bring about the desired therapeutic effect.

Depending on the solubility of the active ingredient in water and/or in an acid medium, this series of processes may occur within very different times and in very different ways

and thus the therapeutic efficacy often manifests itself after an excessively long period of time after the moment of administration: the entire series of processes in question generally indicated by the initials ADME (absorption, distribution, metabolism and elimination) and above all the time interval necessary for the occurrence of the first two
5 (absorption and distribution) may impede or reduce drastically the therapeutic efficacy of a preparation intended to remedy acute painful symptoms.

As already mentioned, the onset of the therapeutic effect of an active substance administered orally is consequently greatly limited by the poor solubility of the drug in an aqueous medium or in gastric and intestinal fluids.

10 Many proposals and solutions have been advanced for overcoming this disadvantage, which is encountered, for example, with many analgesic and non-steroidal anti-inflammatory drugs (so-called NSAID), such as, for example, the preparation of cyclodextrin complexes or the preparation of active ingredients coated with or contained in suitable supports capable of improving the rate of dissolution and thus
15 promoting absorption.

These complexes and derivatives, although they exhibit improved solubility and, at the same time, improved bioavailability characteristics, are nevertheless characterised by the fact that the formation of the complex generally involves the use of equimolar ratios between the active ingredient and the cyclodextrin or substantial amounts of
20 excipients for promoting the solubilisation of the active ingredient.

These technological measures can bring about a substantial increase in the molecular weight and this weight increase can affect finished pharmaceutical forms which, with the same content of active ingredient, are difficult to administer and/or at any rate are not readily accepted by the patient.

25 In any case, the main demand made of a tablet and/or at any rate a solid pharmaceutical form for the oral administration of an analgesic drug is that its administration should bring about the rapid mitigation, if not the disappearance, of the painful symptom; in addition to that demand, another important requirement is that it should be possible to prolong the effect over time, thereby also permitting a substantial simplification of the
30 daily dosage.

In the context of the solution to these problems, a large number of forms have been described and/or developed in the past, including:

- patent USA 2,951,792 (lipid matrix);
- British patent 2,230,185 (double-layered tablet);
- international patent application WO-A-88 08299;
- international patent application WO-A-95 01781 which describes a double-layered
5 tablet of which the two layers contain different doses of the same active ingredient
which is then released at quite different rates.
- international patent application WO-A-94 05277 describing a controlled release
double-layered tablet which contains sodium naproxen in the immediate release layer
and acid naproxen in the delayed release one, said acid naproxen layer comprising an
10 immediate release granulate of acid naproxen and a delayed release granulate one
compressed together, both layers being provided in a lipidic matrix.

It has now been found, and this forms the subject-matter of the present invention, that,
by using a particular solid pharmaceutical form having two component fractions and by
using novel measures in the formulation of an active ingredient which, as such, is
15 poorly soluble in water, it is possible to obtain a solid pharmaceutical form which is
characterised by:

- a rapid and complete disintegration of one of the two component fractions and by an
equally rapid dissolution of the active ingredient contained in said fraction in the form
of a derivative, for example a very soluble salt, which rapidly brings about high plasma
20 levels and the consequent manifestation of the desired therapeutic effect;
- a slow and progressive disintegration or solubilisation of the second fraction of the
pharmaceutical form and by a likewise slow and programmable process of dissolution
of the active ingredient contained as such, that is to say, in non-derivative form, in the
second fraction so as to bring about a prolonged and constant maintenance of efficient
25 drug plasma levels and thus a prolonged therapeutic effect.

The novel pharmaceutical form is above all intended for the administration of an active
ingredient that is to act immediately after administration and that is capable of
maintaining the therapeutic efficacy for a prolonged period of time, ie. that is capable
of bringing about immediately a high level in the blood and the consequent appearance
30 of the therapeutic effect within a very limited time interval and of maintaining this
efficient activity for a prolonged period of time.

The present invention is preferably used in the formulation of non-steroidal anti-

inflammatory drugs and, more generally, for the administration of analgesic drugs exhibiting poor solubility.

By the use of established production techniques and novel formulation criteria as well as special excipients, the present invention also makes it possible to obtain solid
5 pharmaceutical forms that can be used for oral administration and that are capable of releasing, completely and within a very short time interval, the active ingredient contained in soluble form therein, in order to obtain a high level of bioavailability, and of maintaining this therapeutic effect for a prolonged period because the poorly soluble active ingredient is released from the second fraction over a prolonged time interval.

10 The novel pharmaceutical form forming the subject-matter of the present invention is characterised in that, in the simplest case, it is formed by a system of two component fractions containing:

(a) in the first fraction, an active ingredient in the form of a soluble derivative (salt, ester, amide or another pharmaceutically acceptable derivative), together with
15 technological excipients and adjuvants enabling the mass to be compressed and/or processed and ensuring an immediate release of the active substance (or active substances if more than one) contained in that fraction;

(b) in the second fraction, the same active ingredient in non-derivative form and characterised by a substantially lower solubility in water and/or aqueous liquids,
20 together with technological excipients and adjuvants which, in this case too, enable the mass to be compressed but which are such that they modulate, in accordance with accurately programmable kinetics and rates, the release of the active substance(s) contained in that fraction.

The invention is therefore characterised in that the same pharmaceutical form contains
25 a pair of active substances of which one component is in salt and/or derivative form or at any rate has a greater solubility, and one component is in non-salt form and is characterised by a limited solubility in water and/or aqueous liquids.

The present invention is also characterised in that, if the active substance has chiral centres in one or both of the fractions, the active ingredient may be contained in
30 racemic form or in enantiomeric form, which is more active.

In the preparation of each of the two above-mentioned component fractions, in addition to the active ingredient and depending on its characteristics of solubility in

water and/or aqueous liquids, polymeric substances capable of modulating, that is to say, accelerating or slowing down, the release of the active ingredient are also used.

The expression "solid pharmaceutical form having two component fractions" is to be understood as meaning both the double-layered tablets, in which each layer corresponds to one of the two component fractions, and also:

- (i) hard gelatin capsules which contain (or into which are introduced) one or more tablets containing one or more active ingredients in salt (and thus soluble) form and one or more tablets containing that active ingredient in non-salt (and thus poorly soluble) form;
- (ii) hard gelatin capsules containing one or more double-layered tablets prepared by the methods mentioned above;
- (iii) hard gelatin capsules into which are introduced different granulates or pelletised systems containing one or more active ingredients, or alternatively the active ingredient in salt and thus soluble form and the same or another active ingredient in non-salt and thus poorly soluble form.

In the case of active ingredients that are poorly soluble in water, such as, for example, p-isobutylphenylpropionic acid (ibuprofen) which forms the subject of some of the examples which follow, the active ingredient contained in the first fraction (which disintegrates and dissolves rapidly) is in salt form, especially in the form of a lysine salt, while in the said second fraction (which disintegrates and dissolves slowly) the same active ingredient is used as such, that is to say, in non-salt form.

The described pharmaceutical form may contain active ingredients such as non-steroidal anti-inflammatory drugs (NSAID) or steroidal anti-inflammatory drugs, sleep-inducing and tranquillising substances, substances having a preventive activity with respect to angina and hypertension attacks, or anti-histamine and anti-asthmatic drugs.

Bearing in mind the chemical characteristics of the active ingredient, it is possible to use salts (with acids, with organic or inorganic bases), esters, amides and in any case derivatives of which the solubility characteristics differ from those of the non-derivative active ingredient.

In the case of non-steroidal anti-inflammatory drugs, such as, for example, ibuprofen, naproxen, ketoprofen, indomethacin, acetylsalicylic acid, mefenamic acid, flufenamic acid, tiaprofenic acid, tolfenamic acid, diflunisal, sulindac, it is possible to use as

soluble derivatives sodium and potassium salts of inorganic bases in general or of organic bases, or amino acids such as glycine, betaine, histidine, lysine, arginine, ornithine, leucine, tyrosine, either in racemic or in optically active form.

Analogously, the active ingredients indicated above can also be used either in racemic
5 form or in one of the more active diastereoisomeric forms.

In the preparation of the rapid-release first component fraction, it is possible to use customary pharmaceutical excipients, such as diluents, binders, disintegrators and all the other materials well known to the person skilled in the art.

As polymeric substances suitable for promoting an immediate disintegration of the
10 rapid-release fraction of the active ingredient, it is possible to use so-called super-disintegrating excipients, such as, for example, crosslinked polyvinylpyrrolidone, crosslinked sodium carboxymethylcellulose, carboxymethyl starch, a copolymer of potassium methacrylate and divinylbenzene, polyvinyl alcohols, starches and their derivatives, beta-cyclodextrin and derivatives of dextrans in general. The polymeric
15 substances constitute from 1.0 to 90% by weight of the fraction.

It is also possible to use in the first fraction other adjuvant substances formed by so-called effervescent mixtures, that is to say, substances capable of producing the rapid disintegration of the tablet or, in this specific case, the first layer, when the pharmaceutical form comes into contact with aqueous liquids and, preferably, with
20 gastric juice.

These substances may include the carbonates and bicarbonates of sodium and of other alkali metals or alkaline earth metals, sodium carbonate glycol and other pharmaceutically acceptable salts capable of producing effervescence in an acid medium.

25 The adjuvants that may be used in the first fraction include pharmaceutically acceptable organic or inorganic substances having acidic or basic characteristics, or buffer mixtures, which are used to maintain, during the dissolution stage, a micromedium having an optimum pH value for the solubilisation of the active substance. It is also possible to use for that purpose amino acids, such as glycine, betaine, histidine, lysine,
30 arginine, ornithine, leucine, tyrosine, either in racemic form or in an optically active form.

In the preparation of the second fraction which is released slowly and/or which is at any rate characterised by an active ingredient release rate which differs from that of the first fraction, it is possible to use natural and/or synthetic or semi-synthetic biocompatible polymeric materials belonging to the class of the so-called gelling and/or
5 erodible hydrophilic polymers capable of slowing down the release of the active ingredient from the second layer.

Especially suitable for the preparation of the slow-release layer are cellulose derivatives and, to be more precise, those selected from the class consisting of hydroxypropylmethylcellulose having a molecular weight of from 1000 to 4,000,000
10 Daltons, hydroxypropylcellulose having a molecular weight of from 1,000 to 2,000,000 Daltons, carboxyvinyl polymer, polyvinyl alcohols, glucans, xanthans, mannans, galactomannans, scleroglucans, alginates, pectins, amylose with different degrees of crosslinking, carboxymethylcellulose and its derivatives, methylcellulose, ethylcellulose and their salts and/or derivatives and, in general, biocompatible and, preferably,
15 biodegradable cellulose derivatives that are acceptable from the pharmaceutical point of view.

Different types of all the classes of polymer mentioned above are on the market and are at any rate available and are characterised by physico-chemical properties that differ especially in respect of solubility and gelling and/or erosion properties.

20 In the case of hydroxypropylmethylcellulose, it is possible to use various types having a molecular weight within the above-mentioned range and having different degrees of substitution.

These classes of hydroxypropylmethylcellulose exhibit different characteristics which is why they can encounter erosion and/or gelling processes on contact with aqueous
25 liquids, which properties are associated with the viscosity exhibited by the polymeric material.

Depending on the solubility characteristics of the active ingredient, it is possible to use mainly gelling or erodible polymer derivatives, also depending on the desired release rate required for the active ingredient contained in the slow- release layer.

30 The quality and quantity of polymeric material can be determined on the basis of the results of in vitro experiments carried out by means of suitable tests.

The polymeric substances may be present in a percentage varying from 5 to 90%

relative to the total weight of the slow-release layer, but preferably in a percentage varying from 30 to 75%.

- It is possible to use as substances for limiting and/or at any rate delaying the release of the active ingredient from the second fraction, in association with or instead of the hydrophilic polymeric substances, hydrophobic excipients or lipophilic substances, such as glyceryl monostearate, glyceryl palmitostearate, glyceryl behenate, hydrogenated castor oil, solid derivatives of other pharmaceutically acceptable vegetable and/or animal oils, waxes, mono-, di- and tri-substituted glycerides and at any rate derivatives and fatty substances capable of modulating the release of the active substance.
- Finally, it is possible to use in both fractions, for example, of double-layered tablets, excipients customarily used in pharmaceutical technology, such as mannitol, lactose, magnesium stearate, talcum, colloidal silica and others, such as glyceryl monostearate, stearic acid, hydrogenated castor oil, waxes, mono-, di- and tri-substituted glycerides and polyoxyethylene glycols having a molecular weight of from 400 to 50,000.
- A film of entero-soluble polymeric material resistant to gastric juices may subsequently be applied to the finished tablets in order to permit the activation of the system only after the tablet has reached the duodeno-intestinal tract. With this method it is also possible to produce pharmaceutical forms intended for release in the intestine and/or colon.
- It is possible to use as polymeric materials for obtaining enteric-coated systems: cellulose acetophthalate, cellulose acetopropionate, cellulose trimellitate, acrylic and methacrylic polymers and copolymers, having different molecular weights and different pH-dependent solubilities. The materials can be applied to the finished pharmaceutical form by means of the conventional film-coating method using solutions in organic solvents or aqueous dispersions and operating in a fluidised bed or vessel in accordance with known techniques.

The entero-soluble materials resistant to gastric juices can also be used in association with retarding polymers.

- The Examples and the results obtained in the experimental forms described clarify the features and functionality of the novel form according to the invention.

In each case, the innovative nature of the embodiment is characterised by the fact that it is possible to obtain the claimed therapeutic system using established methods of

production currently in use, that is to say, the system can be converted directly to an industrial scale.

The following Examples illustrate in non-limiting manner some solid pharmaceutical forms produced in accordance with the invention.

- 5 Example 1: Double-layered tablet containing 200 mg of ibuprofen of which a quantity corresponding to 100 mg (in the form of lysinised ibuprofen) is contained in the rapid-release first layer and 100 mg in the form of ibuprofen are contained in the second layer that is to release the active ingredient slowly.

- 1 - a - Preparation of the granulate which constitutes the rapid-release first layer containing ibuprofen in lysinised form as active ingredient. (Granulate A)

lysinated ibuprofen	175.0 mg
(equivalent to 100.0 mg of ibuprofen)	
corn starch (intragranular)	40.0 mg
methylcellulose	1.0 mg
15 corn starch (extragranular)	20.0 mg
carboxymethyl starch	16.0 mg
crosslinked polyvinylpyrrolidone	6.0 mg
magnesium stearate	3.2 mg
colloidal silica	1.3 mg
20 total	262.5 mg

- The lysinated ibuprofen and the first amount of corn starch (intragranular) are mixed and the mixture is wetted with a 1.3% aqueous methylcellulose solution until a homogeneously wetted mass is obtained. The moist mass is forced through a 25 mesh sieve and the granulate obtained is dried to constant weight in an oven and passed
25 through the same sieve again. The second amount of corn starch (extragranular), the carboxymethyl starch, the crosslinked polyvinylpyrrolidone, the magnesium stearate and the colloidal silica are added and mixed in for 15 minutes in a Turbula.

A granulate is thus obtained which has good flow and compacting properties. The granulate is then subjected to the compression stage.

- 30 1 - b - Preparation of the granulate which constitutes the slow-release second layer containing ibuprofen in acid form as the active ingredient. (Granulate B)

ibuprofen	100.0 mg
-----------	----------

	mannitol	30.0 mg
	hydroxypropylmethylcellulose	
	(Methocel K 15M)	50.0 mg
	polyvinylpyrrolidone	15.0 mg
5	magnesium stearate	2.0 mg
	talcum	3.0 mg
	colloidal silica	1.0 mg
	total	201.0 mg

The ibuprofen, the mannitol and the hydroxypropylmethylcellulose are mixed and the mixture is wetted with a 10% polyvinylpyrrolidone solution until a homogeneously wetted mass is obtained. The moist mass is forced through a 25 mesh sieve and the granulate obtained is dried to constant weight in an oven and passed through the same sieve again. The magnesium stearate, the talcum and the colloidal silica are added and mixed in for 15 minutes in a Turbula.

A granulate is thus obtained having good flow and compacting properties. The granulate is then subjected to the compression stage.

1 - c - Preparation of the finished tablets

A Layer-press rotary tableting machine (Manesty- Liverpool UK) or an equivalent machine capable of producing multi-layered tablets is used for the preparation of the tablets. As is known to the person skilled in the art, this machine is a rotary tableting machine which has two or three charging stations and which is thus capable of producing two-layered or three-layered tablets; in this particular case, the machine is adjusted to produce two-layered tablets.

The machine used is equipped with oblong stamps (capsule-type of 16 x 6 mm).

The first charging hopper is filled with the granulate described at point 1-a (granulate A) while the second hopper is filled with the granulate described at point 1-b (granulate B).

The first charging station is adjusted to produce layers of 262.5 mg of granulate A (equivalent to 175 mg of lysinised ibuprofen, that is to say, equivalent to 100 mg of ibuprofen), while the second charging station is adjusted to provide a quantity of granulate B (with slow release of the active ingredient) of 201 mg (equivalent to 100 mg of ibuprofen).

By proceeding as described above, tablets having an average weight of 463.5 mg are obtained which contain a total of 200 mg of ibuprofen.

These finished systems are subjected to the dissolution test described below.

1 - d - Dissolution test (in vitro test) In order to evaluate the release characteristics of the finished systems, the apparatus 1, basket (described in USP XXII) is used, operating at 100 rpm and using as the dissolving fluid 1000 mL of simulated intestinal fluid (without enzymes) according to U.S.P. having a pH of 7.5 at 37°C.

The release of the active ingredient is monitored by U.V. spectrophotometric determination at 223 nm, using an automatic system of sampling and quantitative determination and an automatic programme for processing the data (Spectracomp 602 manufactured by Advanced Products-Milan).

The results of the experiments carried out are indicated in Table 1.

TABLE 1

	Time (min.)	mg of ibuprofen released
15	5	101.2
	15	108.9
	30	117.2
	60	132.1
	120	151.2
20	240	178.5
	360	202.8
	420	203.4

It is clear that, of the 200 mg of active ingredient contained in the carrier, approximately 100 mg are released rapidly, within 15 minutes, while the second portion of 100 mg is released within approximately 6 hours.

1 - e - Bioavailability test (in vivo test on a healthy volunteer)

In order to evaluate the bioavailability characteristics of the active ingredient of the novel pharmaceutical form, the tablets described at point 1-c are administered to two healthy volunteers under rigorously controlled conditions.

The bioavailability of the active ingredient is followed by determining the plasma levels obtained, the values of which are indicated in Table 2 (mean values from the two volunteers).

TABLE 2

	Time	mcg/ml
	15	5.2
	30	13.0
5	60	17.8
	120	16.0
	180	10.7
	240	7.9
	360	4.2
10	480	2.1
	720	0.7

Example 2: Comparative example

In order to evaluate the effective therapeutic efficacy of the invention a system analogous to that described in Example 1 was prepared for comparative purposes, but the layer described at point 1-a was replaced by a granulate containing the active ingredient ibuprofen in non-salt form and an identical formulation was used as regards technological excipients and adjuvants. Therefore the tablet involved is, especially, a double-layered tablet containing 200 mg of ibuprofen of which an amount corresponding to 100 mg of ibuprofen is contained in the rapid-release first layer and 100 mg of ibuprofen are contained in the second layer that is to release the active ingredient slowly (the second layer thus having the composition described at point 1-b).

2 - a - Preparation of the granulate which constitutes the rapid-release first layer containing 100 mg of ibuprofen as active ingredient. (Granulate C)

The composition of this granulate and the method of preparation are the same as those already indicated in Example 1, except that, instead of 175.0 mg of lysinised ibuprofen, 100.0 mg of ibuprofen are used.

2 - b - Preparation of the granulate which constitutes the slow-release second layer containing ibuprofen in acid form as the active ingredient.

Starting from the same composition, the same procedure as indicated at point 1-b of Example 1 is used.

2 - c - Preparation of the finished systems (by compression)

The procedure of Example 1-c is repeated.

By operating as described above, tablets having an average weight of 388.5 mg and containing a total of 200 mg of ibuprofen are obtained.

The finished tablets are subjected to the dissolution test.

2 - d - Dissolution test (in vitro test)

- 5 The experiment is carried out using the same apparatus and the same methods as those described above (Example 1-d).

The results of the experiments carried out are indicated in Table 3.

TABLE 3

	Time (min.)	mg of ibuprofen released
10	5	8.7
	15	24.5
	30	52.6
	60	84.2
	120	105.8
15	180	124.6
	240	142.1
	360	172.4
	420	183.1
	480	196.7
20	600	203.5

It is clear that, of the 200 mg of active ingredient contained in the carrier, 100 mg are released within 90 to 120 minutes while the second portion of 100 mg is released within approximately 6 hours.

2 - e - Bioavailability test (in vivo test on a healthy volunteer)

- 25 The bioavailability test, followed by determining the resulting plasma levels, of the active ingredient of the tablets of Example 2-c was carried out by comparison by administering to the same subjects (after the necessary wash-out period) either the formulation described at point 1-c (Example 1) or that of Example 2-c, thus having an identical dosage of the active ingredient.

- 30 The results obtained are indicated in Table 4

TABLE 4

Time	mcg/ml	mcg/ml
------	--------	--------

	(Example 1)	(Example 2)
15	5.2	0
30	13.0	7.8
60	17.8	13.1
5 120	16.0	10.1
180	10.7	8.0
240	7.9	6.5
360	4.2	4.2
480	2.1	1.9
10 720	0.7	0.9

The results indicated in the Table clearly demonstrate the more rapid generation of high plasma levels as a result of the administration of the pharmaceutical form containing the lysine salt of ibuprofen (Example 1) in the first layer compared with the comparative pharmaceutical form containing an identical amount of non-salt form ibuprofen (Example 2) in the first layer. In addition, the plasma concentrations obtained with the formulation of Example 1 remain high for a longer interval of time than do those obtained with the formulation of Example 2.

This result is entirely in line with the aims of the invention.

EXAMPLE 3: Double-layered tablet containing 500 mg of naproxen of which a quantity corresponding to 200 mg (in the form of betainated naproxen) is contained in the rapid-release first layer and 300 mg in the form of naproxen are contained in the second layer which is to release the active ingredient slowly.

3 - a - Preparation of the granulate which constitutes the rapid-release first layer containing naproxen in betainated form as active ingredient. (Granulate D)

betainated naproxen	301.7 mg
(equivalent to 200.0 mg of naproxen)	
corn starch (intragranular)	40.0 mg
methylcellulose	1.0 mg
30 corn starch (extragranular)	20.0 mg
carboxymethyl starch	16.0 mg
polyvinylpyrrolidone	6.0 mg

magnesium stearate	3.2 mg
colloidal silica	1.3 mg
total	389.2 mg

The betainated naproxen and the first amount of corn starch (intragranular) are mixed and the mixture is wetted with a 1.3% aqueous methylcellulose solution until a homogeneously wetted mass is obtained. The moist mass is forced through a 25 mesh sieve and the granulate obtained is dried to constant weight in an oven and is passed through the same sieve again. The second amount of corn starch (extragranular), the carboxymethyl starch, the crosslinked polyvinylpyrrolidone, the magnesium stearate and the colloidal silica are added and mixed in for 15 minutes in a Turbula.

A granulate is thus obtained which exhibits good flow and compacting properties. The granulate is then subjected to the compression phase.

3 - b - Preparation of the granulate which constitutes the slow-release second layer containing naproxen in acid form (300 mg) as the active ingredient. (Granulate E)

naproxen	300.0 mg
mannitol	30.0 mg
hydroxypropylmethylcellulose (Methocel K4M)	50.0 mg
polyvinylpyrrolidone	15.0 mg
magnesium stearate	2.0 mg
talcum	3.0 mg
colloidal silica	1.0 mg
total	401.0 mg

The naproxen, the mannitol and the hydroxypropylmethylcellulose are mixed and wetted with a 10% polyvinylpyrrolidone solution until a homogeneously wetted mass is obtained. The moist mass is forced through a 25 mesh sieve and the granulate obtained is dried to constant weight in an oven and passed through the same sieve again.

The magnesium stearate, the talcum and the colloidal silica are added and mixed in for 15 minutes in a Turbula.

A granulate is thus obtained which exhibits good flow and compacting properties. The granulate is subjected to the compression stage as described above.

3 - c - Preparation of the finished systems (by compression)

The same procedure as that used in Example 1-c is used for the preparation of the tablets.

By operating as described above, tablets are obtained which have an average weight of 790.2 mg (389.2 mg constituting the first layer equivalent to 200 mg of naproxen and 401.0 mg constituting the second layer equivalent to 300 mg of naproxen) and which contain a total of 500 mg of naproxen and which are subjected to the dissolution test.

3 - d - Dissolution test (in vitro test)

By proceeding as described in Example 1-d (using 1000 ml of distilled water as the dissolving fluid and operating at 265 nm in order to determine the active ingredient) the results indicated in Table 6 are obtained.

TABLE 6

Time (min.)	mg of naproxen released
5	82.5
15	202.3
30	253.6
60	337.8
120	380.4
240	445.1
360	485.0
420	507.2

It is clear that, of the 500 mg of active ingredient contained in the carrier, 200 mg are released rapidly, within 15 minutes, while the second portion of 300 mg is released within approximately 6-7 hours.

Example 4: Double-layered tablet containing 200 mg of R(+) ibuprofen of which an amount corresponding to 100 mg, in the form of R(+) sodium ibuprofen, is contained in the rapid-release first layer and 100 mg in the form of R(+) ibuprofen acid are contained in the second layer which is to release the active ingredient slowly.

4 - a - Preparation of the granulate which constitutes the rapid-release first layer (effervescent) containing R(+) sodium ibuprofen as the active ingredient. (Granulate F)

R(+) ibuprofen sodium dihydrate 128.2 mg
(equivalent to 100.0 mg of ibuprofen)

	corn starch	40.0 mg
	polyvinylpyrrolidone	8.0 mg
	citric acid	20.0 mg
	modified sodium bicarbonate	10.0 mg
5	stearic acid	3.0 mg
	colloidal silica	1.5 mg
	total	210.7 mg

The R(+) sodium ibuprofen is mixed with the amount of corn starch and citric acid provided for and the whole is wetted with a 10% w/v polyvinyl-pyrrolidone solution in ethanol until a homogeneously wetted mass is obtained. The moist mass is forced through a 25 mesh sieve and the granulate obtained is dried to constant weight in an oven and is passed through the same sieve again. The modified sodium bicarbonate, the stearic acid and the colloidal silica are added and mixed in for 15 minutes in a Turbula.

A granulate is thus obtained which exhibits good flow and compacting properties. The granulate (granulate F) is then subjected to the compression stage.

4 - b - Preparation of the granulate constituting the second layer which has a release function and contains R(+) ibuprofen acid as the active ingredient. (Granulate G)

	R(+) ibuprofen acid	100.0 mg
20	mannitol	30.0 mg
	hydroxypropylmethylcellulose (Methocel K15M)	50.0 mg
	polyvinylpyrrolidone	15.0 mg
	magnesium stearate	2.0 mg
25	talcum	3.0 mg
	colloidal silica	1.0 mg
	total	201.0 mg

The R(+) ibuprofen acid, the mannitol and the hydroxypropylmethylcellulose are mixed and the whole is wetted with a 10% polyvinylpyrrolidone solution until a homogeneously wetted mass is obtained. The moist mass is forced through a 25 mesh sieve and the granulate obtained is dried to constant weight in an oven and passed through the same sieve again. The magnesium stearate, the talcum and the colloidal

silica are added and mixed in for 15 minutes in a Turbula.

A granulate (granulate G) is thus obtained which exhibits good flow and compacting properties. The granulate is then subjected to the compression stage.

4 - c - Preparation of the finished systems (by compression)

- 5 By operating as described above (Example 1-c), tablets having an average weight of 411.7 mg and containing a total of 200 mg of R(+) ibuprofen are obtained and are subjected to the dissolution test.

4 - d - Dissolution test (in vitro test)

By operating as described in Example 1-d, the results indicated in Table 7 are obtained.

10 TABLE 7

Time (min.)	mg of ibuprofen released
5	68.9
15	97.8
30	116.5
15 60	124.7
120	147.0
240	169.4
360	190.6
420	204.6

- 20 It is clear that, of the 200 mg of active ingredient contained in the carrier, 100 mg are released rapidly, within 15 minutes, while the second portion of 100 mg is released within approximately 6 hours.

Example 5 - Comparative test

- 25 In order to demonstrate the improvement and the greater effectiveness of the present invention over the compositions described in the already cited PCT application n. WO-A-94 05277, an in vivo comparative pharmacokinetic test has been carried out. For this purpose, a formulation was prepared according to the before described examples, consisting of a first immediate release layer containing sodium naproxen and a second delayed release layer containing naproxen. The formulation had the here-below reported composition:
- 30

First (sodium naproxen) layer

sodium naproxen: 235.50 mg (equivalent to 215 mg of naproxen)

	corn starch (intragranular):	43.02 mg
	alluminum lake yellow:	0.02 mg
	methylcellulose:	1.08 mg
	sodium starch glycolate:	17.20 mg
5	crosslinked polyvinylpyrrolidone:	6.44 mg
	corn starch (extragranular):	21.50 mg
	magnesium stearate:	3.44 mg
	silicon dioxide:	1.40 mg
10	Second (naproxen) layer	
	acid naproxen:	500.00 mg
	hydroxypropylmethylcellulose:	50.00 mg
	mannitol:	100.00 mg
	polyvinylpyrrolidone:	16.70 mg
15	talc:	30.00 mg
	magnesium stearate:	4.00 mg
	silicon dioxide:	1.70 mg

20 This pharmacokinetic test has been performed on three healthy volunteers, the naproxen
hemetic levels being monitored over a period of 72 hours; the results are reported in
table 8.

TABLE 8

	Column 1	Column 2	Column 3
Time (hours)	$\mu\text{g/ml}$	$\mu\text{g/ml}$	$\mu\text{g/ml}$
0.0	00.00	00.00	00.00
0.3	24.82		34.20
0.5	39.57	37.00	
0.6			41.70
0.8	52.96		
1.0	56.11	49.80	50.20
2.0	70.62	57.10	57.40

3.0	76.13	59.70	63.00
4.0	78.88	59.40	61.10
6.0	65.75	50.60	56.10
8.0	68.55	44.50	50.80
12.0	51.55	35.70	45.30
24.0	27.14	21.60	33.00
48.0	11.01	07.70	13.50
72.0	04.96	03.20	05.70

In column 1 it is reported the average of the values of the hematic levels of the three single volunteers; in column 2 and 3 the hematic levels of naproxen corresponding to the formulations respectively of examples 2 and 3 of the above cited PCT application are reported.

To better appreciate the differences between the formulation according to the present invention and those of the prior art, the above data have been transferred into fig. 1, from which it is clear that by using the formulation of the present invention higher immediate hematic naproxen levels can be obtained.

Moreover, it must be pointed out that the tablets according to the present invention, besides being more effective than those of the prior art, are also manufactured by means of easier and more consolidated production technologies, with the consequent advantages from the economical point of view.

Example 6

Comparative tests have also been carried out in order to show the greater effectiveness of the formulations of the present invention if compared to those commercially available. For this purpose a tablet, Ibuprofen based has been prepared, having the here-below indicated composition.

Inbuprofen sodium layer

sodium ibuprofenen:	336.00 mg (equivalent to 300 mg of ibuprofen)
methylcellulose:	1.05 mg
starch:	150.00 mg
sodium lauryl sulphate:	0.75 mg

- | | | |
|----|---|-----------|
| | crosslinked polyvinylpyrrolidone | 9.00 mg |
| | dye (E 124): | 0.15 mg |
| | sodium carboxymethylstarch: | 24.00 mg |
| | magnesium stearate: | 4.05 mg |
| 5 | colloidal silica: | 2.00 mg |
| | cellulose (Avicel PH 101): | 62.00 mg |
| | calcium carbonate: | 30.00 mg |
| | talc: | 20.00 mg |
| 10 | Ibuprofen layer | |
| | acid ibuprofen (micronized): | 500.00 mg |
| | methylcellulose: | 50.00 mg |
| | mannitol: | 100.00 mg |
| | polyvinylpyrrolidone: | 16.70 mg |
| 15 | talc: | 35.00 mg |
| | magnesium stearate: | 8.04 mg |
| | colloidal silica: | 1.07 mg |
| | polyethylenglycol: | 5.00 mg |
| 20 | A pharmacokinetic test has then been carried out comparing the hematic levels of Ibuprofen obtained with the above-described tablets with those of two Ibuprofen containing tablets normally available in Switzerland (Brufen ®) and in germany (Anco ®) and having the same Ibuprofen content (800 mg). The results are reported in figure 2 as the mean values of the hematic levels of three single volunteers. From figure 2 it | |
| 25 | is possible to see how higher is the immediate bioavailability of Ibuprofen which can be obtained with the tablets of the present invention. | |

Example 7

Another comparative test, as described in the previous example, has also been conducted with tablets having the here-below reported composition.

30

Ibuprofen sodium layer

sodium ibuprofen: 504.00 mg (equivalent to 450 mg of ibuprofen)

	methylcellulose:	1.60 mg
	starch:	220.00 mg
	sodium lauryl sulphate:	1.12 mg
	polyvinylpyrrolidone XL:	13.50 mg
5	sodium carboxymethylstarch:	36.00 mg
	magnesium stearate:	6.00 mg
	cellulose (Avicel PH 101):	93.00 mg
	talc:	10.00 mg
10	Ibuprofen layer	
	acid ibuprofen:	50.00 mg
	methylcellulose:	5.00 mg
	lactose:	10.00 mg
	polyvinylpyrrolidone:	1.60 mg
15	talc:	3.50 mg
	magnesium stearate:	0.80 mg
	polyethylenglycol:	0.50 mg

20 The hematic levels have been compared to those obtained using tablets normally available on the italian market (Brufen ® and Retard ®); from the result reported in figure 3 the same conclusions can be made. In figure 4 it is also reported the result of a dissolution test.

It is clear that, if an active ingredient is soluble in the form in which it is normally available or obtained, it will be used as such in the first portion, that is to say, that
25 intended for immediate release, while in the programmed slow-release second fraction it will be used in the form of a less soluble derivative or with one of the formulations known for prolonged release.

Finally, it should be noted that the above examples refer to double-layered tablets which constitute the preferred embodiment of the invention, it being understood that
30 other embodiments are provided for, such as those mentioned above and especially capsules containing both the above-mentioned fractions.

CLAIMS

1. Solid pharmaceutical form for the oral administration of at least one active ingredient, with release of the latter at successive times and at different rates, characterised in that it comprises at least two fractions, of which:
 - (a) in the first fraction, the active ingredient is contained in the form of a soluble derivative together with technological excipients and adjuvants enabling the mass to be compressed and/or processed and ensuring an immediate release of the active ingredient (or active ingredients if more than one) contained in that fraction;
 - (b) in the second fraction, the same active ingredient is contained in non-derivative form, characterised by a substantially lower solubility in water and/or aqueous liquids, together with technological excipients and adjuvants which, in this case too, enable the mass to be compressed but which are such that they modulate, in accordance with accurately programmable kinetics and rates, the release of the active ingredient(s) contained in that fraction.
2. Solid pharmaceutical form according to Claim 1, characterised in that the said at least one active ingredient is selected from:
 - (i) steroidal and non-steroidal anti-inflammatory drugs;
 - (ii) sleep-inducing and tranquillising substances;
 - (iii) substances active in the prevention of angina attacks and hypertension attacks;
 - (iv) anti-histamine and anti-asthmatic substances.
3. Solid pharmaceutical form according to Claim 2, characterised in that the anti-inflammatory drug is selected from ibuprofen, ketoprofen, acetylsalicylic acid, mefenamic acid, flufenamic acid, tiaprofenic acid, tolfenamic acid, diflunisal, piroxicam, naproxen, flurbiprofen, sodium diclofenac and indomethacin.
4. Solid pharmaceutical form according to Claim 2, characterised in that the salts of sodium, potassium or inorganic or organic bases of the anti-inflammatory compounds are used as the soluble derivatives of those compounds.
5. Solid pharmaceutical form according to Claim 4, characterised in that the derivatives are glycine, betaine, histidine, lysine, arginine, ornithine, leucine, tyrosine salts either in racemic form or in optically active form.

6. Solid pharmaceutical form according to Claim 2, characterised in that the sleep-inducing and tranquillising substance is selected from diazepam, nitrazepam, clonazepam and oxazepam.
7. Solid pharmaceutical form according to Claim 2, characterised in that the anti-angina and anti-hypertensive substance is selected from diltiazem, urapidil, trapidil, benzydaron and dipiridamol.
8. Solid pharmaceutical form according to Claim 2, characterised in that the anti-histamine or anti-asthmatic substance is selected from terfenadin, chlorpheniramine, terbutaline and combinations thereof.
9. Solid pharmaceutical form according to Claim 1, characterised in that the adjuvant substances contained in the first component fraction are selected from the group of the natural and/or synthetic and/or semi-synthetic polymers belonging to the class of the disintegrators and/or super-disintegrators.
10. Solid pharmaceutical form according to Claim 9, characterised in that the polymers are selected from crosslinked polyvinylpyrrolidone, crosslinked sodium carboxymethylcellulose, carboxymethyl starch, a copolymer of potassium methacrylate and divinylbenzene, polyvinyl alcohols, starches and their derivatives, microcrystalline cellulose and derivatives of cellulose, beta-cyclodextrin and derivatives of dextrin in general.
11. Solid pharmaceutical form according to Claim 10, characterised in that the polymers are present in the first fraction in an amount of from 1.0 to 90% by weight based on the weight of the fraction.
12. Solid pharmaceutical form according to Claim 11, characterised in that the polymers are present in the first fraction in an amount of from 20 to 70% by weight based on the weight of the fraction.
13. Solid pharmaceutical form according to Claim 1, characterised in that the adjuvant substances acting as diluents are selected, depending on the hydrophilic characteristics of the active ingredient, from the group consisting of starch, pregelled starch, calcium phosphate, mannitol, lactose, saccharose, glucose, sorbitol and microcrystalline cellulose.

14. Solid pharmaceutical form according to Claim 1, characterised in that the adjuvant substances acting as agglutinants are selected from the group of polymers having a binding power.
15. Solid pharmaceutical form according to Claim 14, characterised in that the polymers are selected from gelatin, polyvinylpyrrolidone, methylcellulose, sizing starch, ethylcellulose, gum arabic and gum tragacanth.
16. Solid pharmaceutical form according to Claim 1, characterised in that the adjuvant substances having the function of promoting the wettability and the solubilisation of the active ingredient are selected from the group consisting of ionic and non-ionic surfactants, saponins and sterols.
17. Solid pharmaceutical form according to Claim 16, characterised in that the substance promoting the wettability and solubilisation of the active ingredient is contained in a percentage of from 0.01 to 25% by weight based on the active ingredient.
18. Solid pharmaceutical form according to Claim 1, characterised in that the adjuvant substances acting as lubricants and anti-adherents are selected from the group consisting of magnesium stearate, stearic acid, colloidal silica, glyceryl monostearate, polyoxyethylene glycols having a molecular weight of from 400 to 50000, hydrogenated castor oil, waxes and mono-, di- and tri-substituted glycerides.
19. Solid pharmaceutical form according to Claim 1, characterised in that the adjuvant substances have an effervescent effect and are selected from the group consisting of carbonate of sodium and/or other alkali metals and/or alkaline earth metals, sodium bicarbonate, sodium carbonate glyccoll and other pharmaceutically acceptable salts capable of producing effervescence in an acid medium, citric acid, tartaric acid and fumaric acid.
20. Solid pharmaceutical form according to Claim 1, characterised in that the adjuvant substances producing effervescence are selected from citric acid, tartaric acid and fumaric acid.
21. Solid pharmaceutical form according to Claims 19 and 20, characterised in that the adjuvant substances having an effervescent effect are present in an amount of from 3 to 40% by weight of the weight of the first fraction.

22. Solid pharmaceutical form according to Claim 1, characterised in that the second fraction contains natural and/or synthetic or semi-synthetic biocompatible polymeric materials belonging to the class of the so-called gelling and/or erodible hydrophilic polymers capable of slowing down the release of the active ingredient from the second fraction.
23. Pharmaceutical form according to Claim 22, characterised in that the hydrophilic polymers are selected from the class consisting of hydroxypropylmethylcellulose having a molecular weight of from 1000 to 2,000,000 Daltons, carboxyvinyl polymer, polyvinyl alcohols, glucans, xanthans, mannans, galactomannans, scleroglucans, alginates, pectin, amylose having different degrees of crosslinking, carboxymethylcellulose and its derivatives, methylcellulose, ethylcellulose and their salts and/or derivatives.
24. Pharmaceutical form according to Claims 22 and 23, characterised in that the polymeric substances may be present in a percentage varying from 5 to 90% relative to the total weight of the slow-release fraction.
25. Pharmaceutical form according to Claims 22 and 23, characterised in that the polymeric substances may be present in a percentage varying from 30 to 75% relative to the total weight of the slow-release fraction.
26. Solid pharmaceutical form according to Claim 1, characterised in that it is in the form of a double-layered tablet of which each layer constitutes one of the component fractions.
27. Solid pharmaceutical form according to Claim 26, characterised in that it contains from 1 to 90% by weight of active ingredient.
28. Solid pharmaceutical form according to Claim 26, characterised in that it contains ibuprofen as the active ingredient, with a dimensional distribution of less than 20 microns.
29. Solid pharmaceutical form according to Claim 26, characterised in that it contains sodium lauryl sulphate as the surfactant substance.
30. Solid pharmaceutical form according to Claim 1, characterised in that it is in the form of a hard gelatin capsule which contains one or more tablets containing at least one active ingredient in a form soluble in water and aqueous liquids and one or more

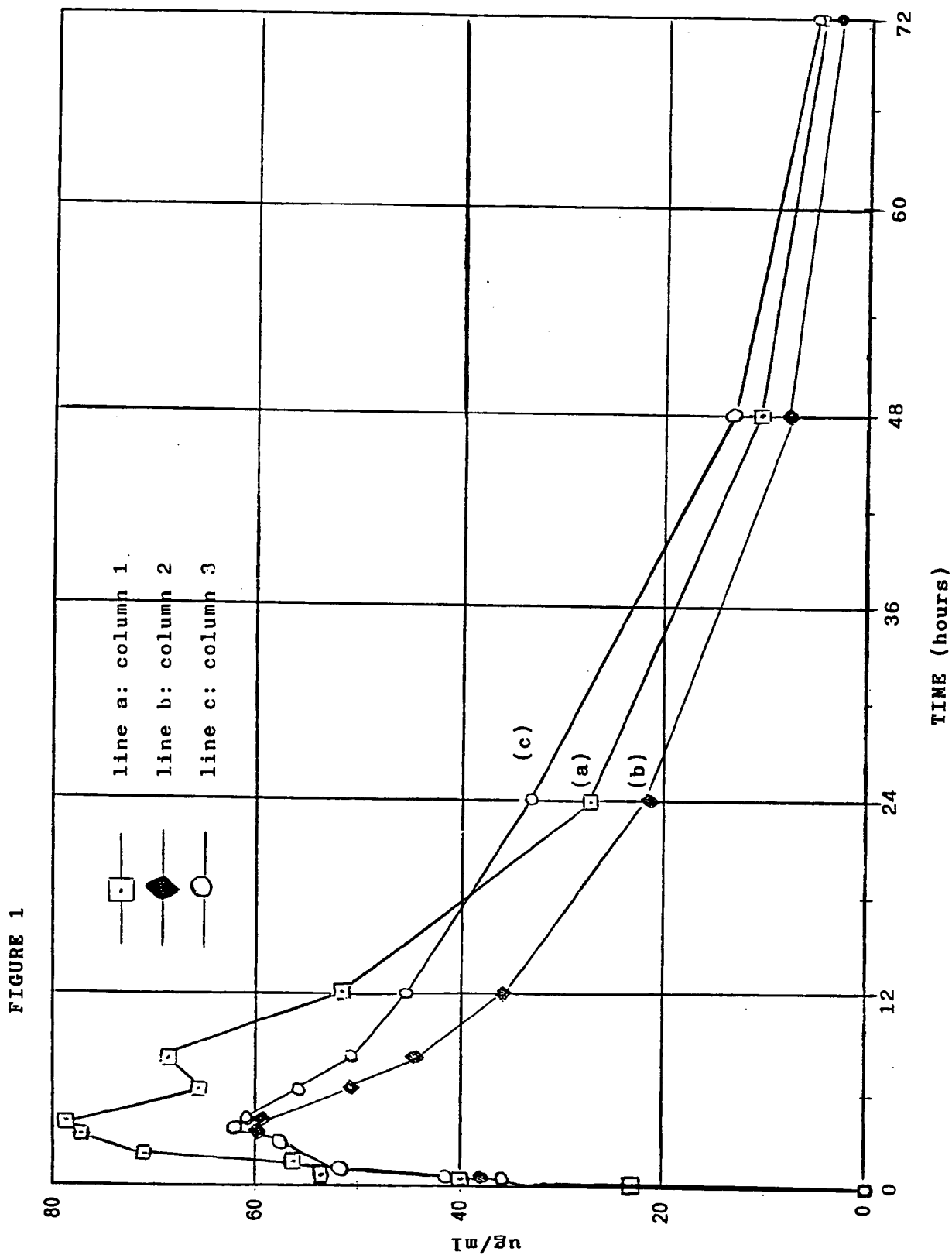
tablets containing the same at least one active ingredient in delayed and programmed release form.

31. Solid pharmaceutical form according to Claim 1, characterised in that it is in the form of a hard gelatin capsule which contains one or more double-layered tablets according to Claim 26.

32. Solid pharmaceutical form according to Claim 1, characterised in that it is in the form of a hard gelatin capsule which contains at least two different granulates of which at least one contains at least one active ingredient in a form readily soluble in water or aqueous liquids and at least one contains the same at least one active ingredient in a delayed and programmed release form.

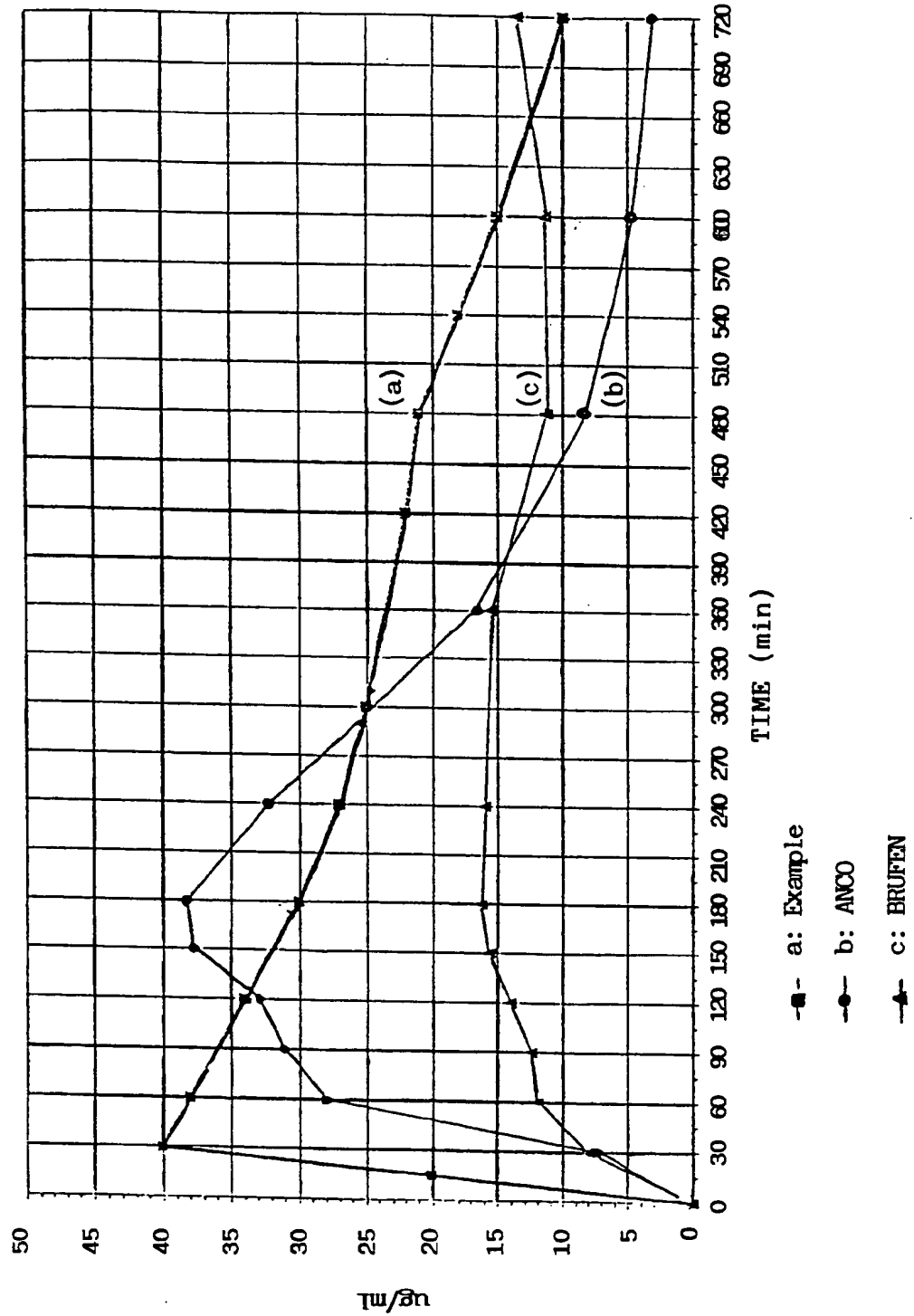
33. Solid pharmaceutical form according to Claim 32, characterised in that the granulates are in pelletised form.

- 1/4 -



- 2/4 -

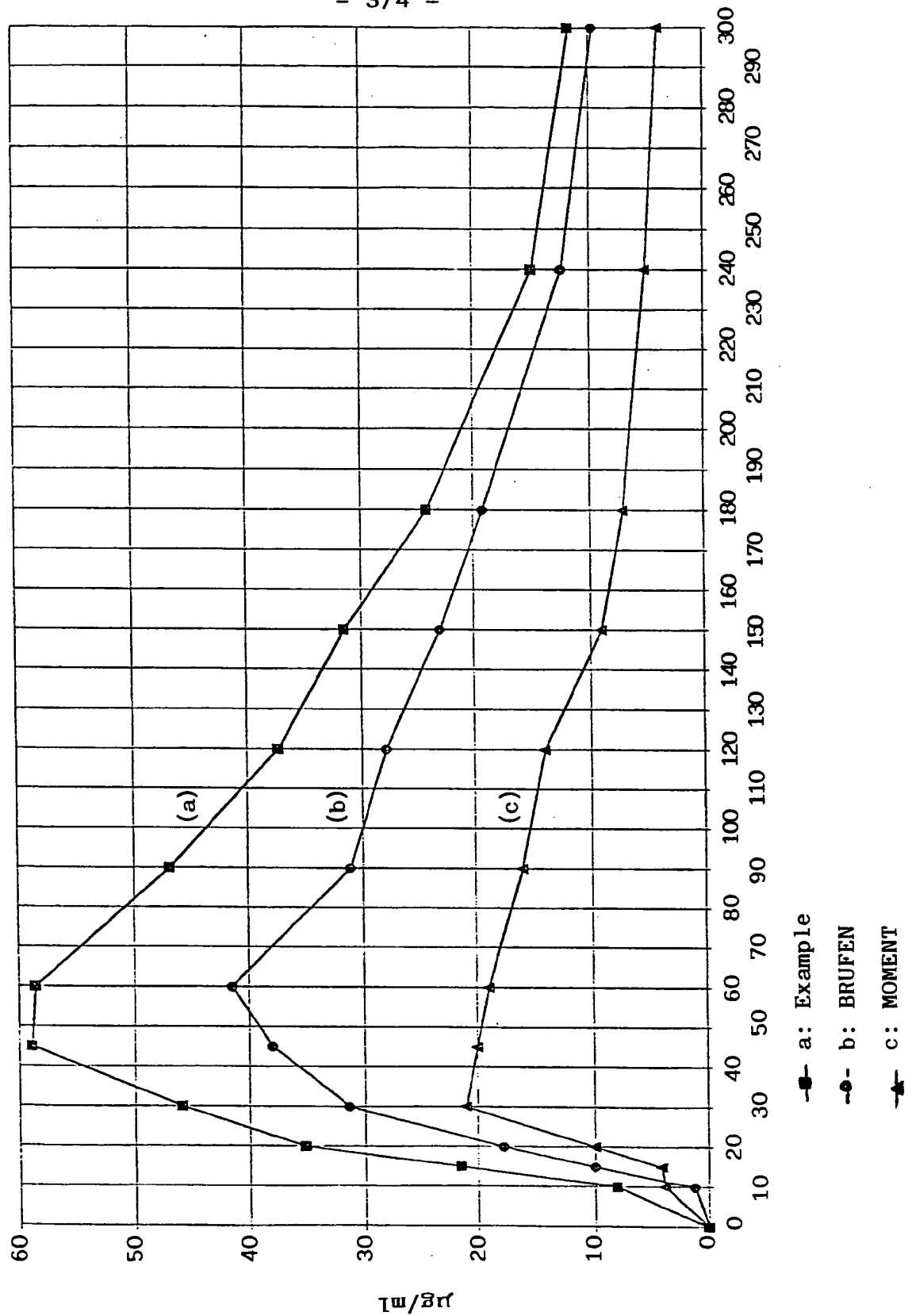
FIGURE 2



SUBSTITUTE SHEET (RULE 26)

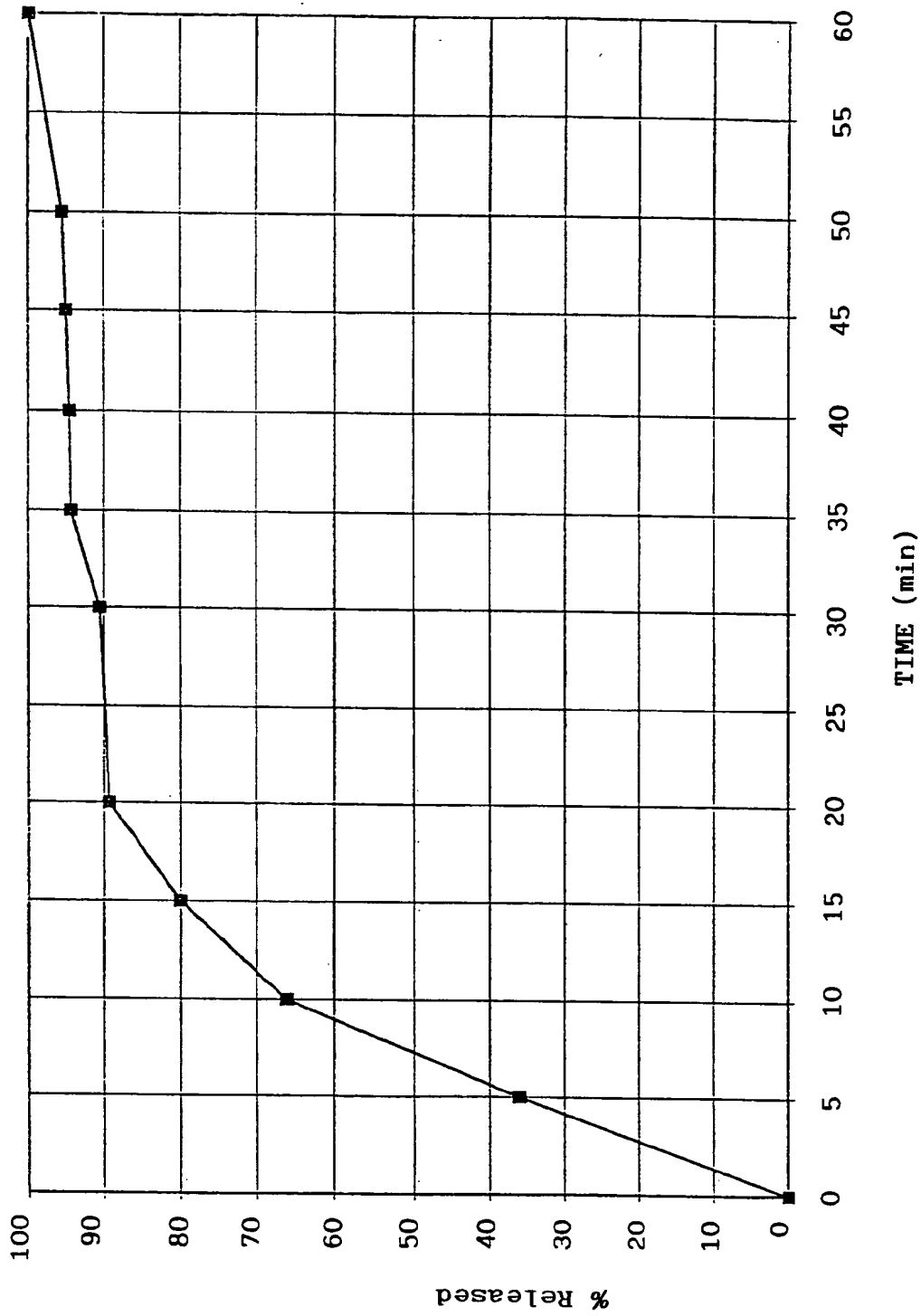
- 3/4 -

FIGURE 3



- 4/4 -

FIGURE 4



INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 96/02495

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/20 A61K9/48 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,95 01781 (APR APPLIED PHARMA RESEARCH SA,CH) 19 January 1995 cited in the application see the whole document ---	1-29
Y	WO,A,94 05277 (SCHIAPPARELLI SEARLE,U.S.A.) 17 March 1994 cited in the application see the whole document ---	1-29
Y	WO,A,94 06416 (JAGOTEC AG,CH) 31 March 1994 see the whole document ---	1-29
Y	WO,A,93 05769 (MARVOLA M.L.,FI) 1 April 1993 see the whole document ---	1-29
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- * "A" document defining the general state of the art which is not considered to be of particular relevance
- * "E" earlier document but published on or after the international filing date
- * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- * "O" document referring to an oral disclosure, use, exhibition or other means
- * "P" document published prior to the international filing date but later than the priority date claimed

- * "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- * "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- * "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * "&" document member of the same patent family

Date of the actual completion of the international search

20 September 1996

Date of mailing of the international search report

03.10.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Scarponi, U

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 96/02495

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 384 514 (NORWICH EATON PHARMACEUTICALS INC.,U.S.A.) 29 August 1990 see the whole document ---	1-29
Y	WO,A,88 08299 (MCNEILAB INC.,U.S.A.) 3 November 1988 cited in the application see the whole document ---	1-29
Y	US,A,5 338 550 (D.E.EDGREN ET AL.) 16 August 1994 see the whole document -----	1-29

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/02495

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9501781	19-01-95	CA-A- 2144167 EP-A- 0659074	19-01-95 28-06-95
WO-A-9405277	17-03-94	AT-T- 135570 AU-A- 2916792 CA-A- 2143010 DE-D- 69209323 DE-T- 69209323 EP-A- 0656776 ES-T- 2084390 JP-T- 8500834	15-04-96 29-03-94 17-03-94 25-04-96 05-09-96 14-06-95 01-05-96 30-01-96
WO-A-9406416	31-03-94	IT-B- 1255522 AU-A- 4818293 CA-A- 2145513 EP-A- 0663820 JP-T- 8501544	09-11-95 12-04-94 31-03-94 26-07-95 20-02-96
WO-A-9305769	01-04-93	FI-B- 93924 AT-T- 135204 CA-A- 2119158 DE-D- 69209080 DE-T- 69209080 EP-A- 0605514	15-03-95 15-03-96 01-04-93 18-04-96 01-08-96 13-07-94
EP-A-384514	29-08-90	US-A- 5032406 AU-B- 632793 AU-A- 4997090 CA-A,C 2010037 DE-D- 69004708 DE-T- 69004708 ES-T- 2060923 IE-B- 63311 IL-A- 93424 JP-A- 3200724	16-07-91 14-01-93 30-08-90 21-08-90 05-01-94 24-03-94 01-12-94 05-04-95 27-02-94 02-09-91
WO-A-8808299	03-11-88	US-A- 4806359 AU-B- 604110 AU-A- 1477488 AU-B- 603675	21-02-89 06-12-90 27-10-88 22-11-90

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/02495

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-8808299		AU-A- 1719788	02-12-88
		CA-A- 1310272	17-11-92
		DE-A- 3865077	31-10-91
		DE-A- 3879080	15-04-93
		EP-A- 0290168	09-11-88
		EP-A- 0312581	26-04-89
		GR-B- 1000019	31-01-90
		HK-A- 22892	03-04-92
		IE-B- 62786	22-02-95
		JP-B- 2519296	31-07-96
		JP-A- 63280021	17-11-88
		JP-T- 1503070	19-10-89
		NO-B- 176203	14-11-94
		NO-B- 175185	06-06-94
		US-A- 5462747	31-10-95
		US-A- 5200193	06-04-93
US-A-5338550	16-08-94	US-A- 5204116	20-04-93

THIS PAGE BLANK (USPTO)